streptokinase-streptodornase, either intramuscularly or by buccal tablets, or the use of oral tablets, is inadequate to establish these products as effective agents for reducing inflammatory reactions. The criteria of physiologic responses by which the systemic dose can be monitored are vague since the doses are below the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent" response in complex multifactorial diseases. Because streptodornase is inactive when given parenterally, the alleged anti-inflammatory effect should be due either to streptokinase activity or to the nonspecific effects of streptococcal proteins on host defenses. Because streptokinase activity by the dose and methods given cannot be demonstrated to be fibrinolytic, the remaining rationale for streptokinase-streptodornase as an anti-inflammatory agent might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of streptokinase-streptodornase as an anti-inflammatory agent.

3. *Thrombolysis.* In contrast to the intramuscular use of streptokinase-streptodornase, recent clinical investigation of highly purified and potent preparations of streptokinase and urokinase have been carried out in the treatment of thromboembolic diseases. Two purified streptokinase preparations have recently been licensed by FDA. An appraisal of clinical efficacy should be considered separately for each of the following indications:

a. *Pulmonary embolism and deep vein thrombosis.* It is difficult to separate these two indications because pulmonary embolism that does not arise from thrombi in the right heart is almost always associated with deep vein thrombosis. In pulmonary embolism the diagnostic tools of angiography ventilation-perfusion lung scans, and selective vascular catheterization have permitted quantification of the effects of thrombolytic agents on pulmonary emboli to an extent not possible with many other lesions. Although all recent studies were not always completely controlled, the universal observation has been more rapid resolution of the embolus than expected with conventional treatment and the parameters of improved functions measured were frequently statistically significant.

Similarly, it has been well demonstrated by venous angiograms in a statistically significant number of selected cases that thrombi in the deep veins of the lower extremity can be lysed and blood flow restored, at least temporarily.

In life-threatening pulmonary embolization, wherein obstruction of the pulmonary circulation is of a severe degree, intravenous streptokinase clearly improves blood flow. What is not yet proven by adequate clinical data is whether such use reduces mortality significantly, reduces subsequent embolization, or reduces damage to the lungs. Similarly, the demonstrated lysis of venous thrombi in the lower extremities does not yet establish that normal venous function has been restored, vascular damage avoided reduced, pulmonaryemboli reduced, or chronic venous insufficiency prevented. Further experience will be necessary to determine the degree of efficacy of intravenous streptokinase in this form of thromboembolic disease. Meanwhile, however, the Panel considers intravenous streptokinase with the licensed products to be effective to the extent described and within the limitations expressed.

b. *Arterial thrombosis*—(1) *Myocardial infarction.* Of nine recent controlled clinical trials (Refs. 3 through 12), three early European trials showed a statistically significant decrease in mortality in patients treated with streptokinase for 18 to 24 hours as compared to controls. In general, trials which only a minority of patients were studied in coronary care units suggested reduced mortality in patients treated with fibrinolytic agents; whereas four controlled randomized trials done entirely in coronary care units failed to verify these findings. Further trials are needed to clarify whether there are true benefits to be derived from treatment of myocardial infarctions with intravenous fibrinolytic agents.

(2) *Peripheral arterial thrombosis.* Although data for efficacy in acute arterial occlusion suggest some effect, especially in the more distal vessels of the lower extremity, the critical and urgent nature of such problems usually demands a surgical approach. Use of thrombolytic agents for peripheral arterial occlusion should probably be limited to clinically important lesions in patients who either are poor surgical candidates or in whom the indications for surgery are not absolute. Adequate data to establish efficacy are not yet available, however.

c. *Retinal diseases.* The reported experience of patients with retinal vascular disease treated with thrombolytic agents is generally anecdotal and insufficient to establish efficacy. Controlled studies with objective, double-blind measurements are, however, underway.

d. *Complications of intravenous thrombolytic therapy.* Fever appears to be a common reaction. A single dose of 100 mg of hydrocortisone intravenously has been administered routinely in several investigative protocols presumably to reduce the febrile and "allergic" responses. No clear evidence for the value of corticosteriods administered this way is available. The nature of the pyrogenic reaction is also not clear. It may be hyperimmune or an endotoxin-like reaction to the streptococcal protein or it may be the result of rapid fibrinolysis. Skin testing in man to determine the local reactivity of the highly purified streptokinase products has not been done systematically.

Clearly allergic reactions (other than fever) have been remarkably few and have been more annoying than serious. A few cases have been reported wherein shock-like reactions resembling sublethal anaphylaxis have occurred. The nature of these are difficult to establish, but on theoretical grounds a rare truly anaphylactic reaction may be anticipated.

Bleeding is common from puncture sites, but serious hemorrhage occurs only occasionally and usually is due to underlying predisposing causes.

Antibodies to streptokinase are stimulated and they may increase refractoriness to repeated doses. More careful studies of these responses and their possible relation to untoward reactions involving immune complexes should be made.

e. *Contraindications of thrombolytic therapy.* These are similar to contraindications of anticoagulant therapy—bleeding disorders, recent surgery, severe hypertension, gastrointestinal ulcers, diabetic retinopathy, and recent cerebrovascular accidents.

Recommendations

For the sake of clarity, the following table relates the recommendations by major category of usage to the licensed products available.

1. *Topical products.* Category I is recommended for the topical use of streptokinase-streptodornase but only if the current labeling is revised to conform with the recommendations detailed above. The value of the suspension of the topical product in carboxymethylcellulose should be documented by further clinical evidence of effectiveness (Category IIIA).

2. The streptokinase-streptodornase products for intramuscular and oral use, including buccal tablets, have not been proved to be effective thrombolytic or anti-inflammatory agents. Category II is recommended for these.

3. The Panel considers the intravenous use of streptokinase with the licensed products to be effective to the extent described and within the limitations expressed. Further intensive investigation of streptokinase and urokinase in thromboembolic disease should be encouraged, bearing in mind that risk-benefit assessments will vary greatly in individual clinical conditions and circumstances.

Efforts to purify or synthesize urokinase should also be encouraged in order to substitute a naturally synthesized human product for a streptococcal protein.

TABLE 1.—STREPTOKINASE-STREPTODORNASE

Indications	Topical		Tablets			Intravenous
	Topical	Jelly	Intramuscular	Buccal	Oral	
1. Debridement:						
a. Body cavities	I (1)					
b. Wounds and fistulae	I (1)	III A				
c. Luminal	I (1)					
2. Anti-inflammatory			II	II	II	
3. Thrombolytic			II	II	II	I

I=Effective.
II=Ineffective.
IIIA=More clinical data required before efficacy can be determined.
—=Not applicable.
(1)=Revise labeling.

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Streptokinase-Streptodornase (Varidase) Buccal Tablets Manufactured by Lederle Laboratories Division, American Cyanamid Co.

The manufacturer did not submit specific information for streptokinase-streptodornase buccal tablets. In its generic review of buccally administered streptokinase-streptodornase, the Panel found no evidence that this product is effective.

Recommendations. The Panel recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Intramuscular, Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* Each vial for intramuscular injection contains 20,000 units of streptokinase and at least 5,000 units of streptodornase with thimerosal 0.2 mL per vial added as a preservative. The production of streptokinase-streptodornase is as described in the Generic Statement. Two milliliters of sterile water for injection of sterile physiologic saline is added to the contents of a vial to make a solution containing 5,000 units of streptokinase per 0.5 mL for intramuscular injection. Procedures employed in the manufacture of Varidase include standards tests for pyrogenicity in animals and sterility.

2. *Labeling*—a. *Recommended use/indications.* Intramuscular use of Varidase is recommended in the treatment of edema associated with infection and trauma. The best results are claimed in infections that do not produce necrosis of tissue such as thrombophlebitis, epididymitis, and cellulitis. A beneficial effect of inflammation and edema with the use of this product is expected in all patients within 2 days after the start of treatment and in a small number of patients within a period of hours. An aggravation of the infection has not been observed in any of the patients but a rise in temperature attributable to streptokinase has been noted in about 10 percent of these patients. No significant change in prothrombin time nor in fibrinolysis can be detected at usual doses recommended. It is recommended that intramuscular use of Varidase be accompanied by the administration systemically of a broad-spectrum antibiotic. The use of the product in patients with abscesses is not a substitute for sound surgical principles.

b. *Contraindications.* Varidase should never be administered intravenously. Varidase should not be injected intramuscularly when there is evidence of a defect in blood coagulation, or where liver function is depressed.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Upon intramuscular injection, the mechanism by which streptokinase produces a reversal of the inflammatory process is not known. The streptodornase in the product is inactive when administered systemically. Parenteral administration has not been considered effective in the treatment of abscesses but is claimed to be effective in a wide variety of inflammatory lesions including bronchopulmonary inflammation (by either aerosol or systemic administration), gangrene from occlusive arterial disease, radiation necrosis, cervicitis, cystitis, pericarditis, osteomyelitis, etc.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No significant untoward reactions reported. Streptokinase and streptodornase are antigenic but allergic reactions are rare. The antibody response may require higher dosage to overcome inhibition of enzyme action but is not harmful.

c. *Benefit/risk ratio.* There is little risk in the use of the product but efficacy has not been demonstrated.

4. *Critique.* The criteria of physiologic responses by which the systemic dose of streptokinase can be monitored are vague since the doses are below the threshold of fibrinolysis. The empirical criteria for beneficial responses are subjective and anecdotal and based on such observations as "improved" or "excellent response" in complex multifactorial disease and unmatched control series. Because streptodornase is inactive when given parenterally and streptokinase activity in the dose given cannot be demonstrated to be fibrinolytic or clearly antithrombotic, the only remaining rationale for streptokinase-streptodornase as anti-inflammatory therapy might be its nonspecific effect as a foreign protein. The latter does not constitute an adequate rationale for the use of

streptokinase-streptodornase as an anti-inflammatory agent.

5. *Recommendations.* The Panal recommends that this product be placed in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Oral Tablets, Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Desciption.* Each tablet contains 1,000 units of streptokinase and 2,500 units of streptodornase. Tablets are marketed as peach-colored, round, flat-faced, beveled tablets scored in half and 1 1/32 inches in diameter. The enzymes are prepared as described in the Generic Statement.

2. *Labeling*—a. *Recommended use/indications.* Varidase oral tablets are recommended for the same indications as the intramuscular preparation and for the reduction of edema and inflammation in the conditions mentioned in the Generic Statement. The average oral dose is 1 tablets (10,000 units of streptokinase) 4 times daily. In acute situations higher doses may be advisable. Normally treatment is continued for 4 to 6 days. Streptodornase is not believed to have therapeutic benefit in oral therapy.

b. *Contraindications.* Contraindicated in patients with reduced plasminogen or fibrinogen.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* Only streptokinase is involved in bringing about the desired clinical effect. The rationale for the use of tablets appears to be twofold: (i) Buccal absorption: Streptokinase is supposed to combine with salivary plasminogen and then to be absorbed by the buccal mucosa in quantities sufficient to convert plasminogen to plasmin. (ii) Intestinal absorption: Gastic juice contains considerable quantities of plasminogen that appears to be activated by streptokinase and absorbed. Claims for clinical efficacy have been discussed in the Generic Statement on streptokinase-streptodornase.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* During the past 5 years there has been only one complaint of a reaction.

c. *Benefit/risk ratio.* There is little risk in the use of the product but benefit has not been demonstrated.

4. *Critique.* In addition to the lack of clear evidence that Varidase is absorbed from the gastrointestinal tract in a form that can produce the physiologic activity of streptokinase, the claims for significant clinical benefit from this route of clinical administration, as in the case of intramuscular therapy, are subjective and anecdotal and do not constitute adequate proof of efficacy.

5. *Recommendations.* The Panel recommends that this product be place in Category II and that the appropriate license be revoked because the product has not been shown to be effective nor is it likely that further clinical investigation will prove it to be so.

Varidase, Topical Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Desciption.* This product is a partially purified mixture of extracelluar enzymes produced from a culture of Group C streptococci grown for about 18 hours in a medium consisting of acid-hydrolyzed casein fortified with sugar, minerals, vitamins, and a reducing substance. The enzymatic actions on fibrin and pus are described in the Generic Statement. Each vial contains 100,000 units of streptokinase and 25,000 units of streptodornase and less than 100 units of streptolysin. The powder is dissolved in 10 to 20 mL of sterile water or normal saline. This dilution gives a solution containing approximately 5,000 to 10,000 units of streptokinase and 1,000 to 2,000 units of streptodornase per mL. The identical product is available in a mixture with 4.5 percent carboxymethylcellulose jelly. Procedures employed in the manufacture of topical Varidase include standard tests for pyrogenicity in animals and sterility.

2. *Labeling*—a. *Recommended use/indications.* This preparation is recommended wherever clotted blood, fibrinous, or purulent accumulations are undesirably present following trauma or infectious processes which have led to ulceration or abscess formation. The action of the enzymes results in the liquefaction of the two main viscous substances in inflammatory and purulent exudates, fibrin, and nucleoprotein. A long list of suppurative conditions are suggested for topical treatment (see Generic Statement) on wounds or by installation in body cavities such as the pleura, pericardium, bladder, sinuses, bronchi, and joints.

b. *Contraindications.* Varidase should not be used in the presence of active hemorrhage and is not intended for and cannot act upon fibrous tissue, mucoproteins, or collagens.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* May be effective for topical and local use in some situations where enhanced liquefaction of pus and fibrin is beneficial and where the products of inflammation can be drained. Such uses are only adjunctive to other medical and surgical procedures. Its substrates must be available and accessible and the enzymes and activators must be in continued contact with their substrates under physiologic conditions of temperature and pH. Its use in body cavities, wounds and fistulae, and luminal areas should be effective only under conditions defined in the Generic Statement.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No reactions have been reported from 1969 through April of 1974 for the use of topical streptokinase-streptodornase by Lederle Laboratories.

c. *Benefit/risk ratio.* Aside from the potential dangers of using this product in closed body cavities without adequate drainage, there is little risk in its topical use and the product is effective when its use is limited to well-defined situations.

4. *Critique.* The local and topical use of streptokinase-streptodornase has some limited efficacy as a method adjunctive to other medical and surgical procedures but only when used strictly in accord with the specific conditions that make the enzymes active—particularly the presence of the proper substrates and the use of a technique adequate to keep the solution in contact with pus and fibrinous exudates for adequate periods of time.

5. *Recommendations.* The Panel recommends that this product be placed in Category I and that the appropriate license(s) be continued provided that labeling is revised in accordance with the recommendations in this Report.

Varidase With Carboxymethylcellulose Jelly Topical Manufactured by Lederle Laboratories Division, American Cyanamid Co.

1. *Description.* This product is identical to Varidase, topical, produced by Lederle Laboratories except for the addition of carboxymethylcellulose jelly, 4.5 percent. The mixture is then packaged in jars of jelly and vials of streptokinase-streptodornase with instructions to prepare a mixture by dissolving the contents of the vial in 5 milliliters of sterile water or normal saline and mixing this volume with the jar of jelly supplied.

2. *Labeling*—a. *Recommended use/indications.* The indications are the same as described for the use of Varidase, topical, when surface applications are made and when the use

of jelly will enhance maintenance of contact between the enzymes and the surface substrates. For application to the hands the jelly containing Varidase may be placed inside a loose rubber glove fastened at the wrist.

b. *Contraindications.* No specific contraindications are noted for the addition of the jelly to topical varidase when used on surfaces as a debridement aid.

3. *Analysis*—a. *Efficacy*—(1) *Animal.* Not applicable.

(2) *Human.* May be effective for topical use in some situations where enhanced liquefaction of pus and fibrin is an aid to debridement and where the maintenance of contact between the enzymes and the substrates on the wounds may be enhanced by the use of a jelly.

b. *Safety*—(1) *Animal.* This product meets Federal requirements.

(2) *Human.* No reactions have been reported through April of 1974 for the topical use of streptokinase-streptodornase.

c. *Benefit/risk ratio.* There is no apparent risk to the topical use of this product and the issue of efficacy is limited to its use in well-defined situations and to the method of maintaining the product in contact to the surface to which it is applied.

4. *Critique.* The topical use of this product may be of some use in the specific situations defined in the Generic Statement when the addition of jelly to the mixture will assist in maintaining enzyme-substrate contact. No clear clinical evidence has been presented, however, that specifically pertains to the advantages of the addition of the jelly to topical solutions of Varidase.

5. *Recommendations.* The Panel recommends that this product be placed in Category IIIA and that the appropriate license be continued for a period not to exceed 3 years during which time the manufacturer shall provide evidence for the effectiveness of this product, provided that the labeling is revised in accordance with the recommendations in this Report.

FDA's Responses to the Panel's Recommendations

A. Regulatory Categories

1. The Panel recommended that bacterial vaccines and toxoids be grouped into regulatory categories as follows:

a. *Category I.*—(1) *Licensed biological products determined to be safe and effective and not misbranded* [and may continue in interstate commerce]: Collagenase, Advance Biofactures Corp., License No. 383; Tetanus Immune Globulin (Human), Armour Pharmaceutical Co., License No. 149; BCG Vaccine, Botulism Antitoxin (Types A, B, and E), Botulism Antitoxin (Type E), Tetanus Toxoid, Connaught Laboratories, Ltd., License No. 73; Plague Vaccine, Tetanus Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Eli Lilly & Co., License No. 56; BCG Vaccine, Glaxo Laboratories, Ltd., License No. 337; Diphtheria Antitoxin, Diphtheria Toxoid Adsorbed, Tetanus Toxoid Adsorbed, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Cholera Vaccine, Tetanus Immune Globulin (Human), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Immune Globulin (Human), Tetanus Toxoid Adsorbed, Typhoid Vaccine, Massachusetts Public Health Biologic Laboratories, License No. 64; Tetanus Immune Globulin (Human), Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Anthrax Vaccine Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Pertussis Vaccine Adsorbed, Typhoid Vaccine, Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Parke-Davis, Division of Warner-Lambert Co., License No. 1; Tetanus Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140; BCG Vaccine, University of Illinois, License No. 188; and Cholera Vaccine, Tetanus Immune Globulin (Human), Typhoid Vaccine (acetone inactivated), Typhoid Vaccine (heat-phenol inactivated), Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category I but for which the product license has been revoked at the manufacturer's request subsequent to the Panel's review.* Diphtheria Toxoid, Connaught Laboratories, Ltd., License No. 73; Tetanus Toxoid, Cutter Laboratories, Inc., License No. 8; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with aluminum phosphate), Tetanus Immune Globulin (Human), Dow Chemical Co., License No. 110; Cholera Vaccine, Pertussis Vaccine, Typhoid Vaccine, Eli Lilly & Co., License No. 56; Streptokinase-Streptodornase (Varidase, Topical), Lederle Laboratories, Division American Cyanamid Co., License No. 17; Cholera Vaccine, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Antitoxin, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Tetanus Immune Globulin (Human), Michigan Department of Public Health, License No. 99; Tetanus Immune Globulin (Human), Oesterreichisches Institut Fuer Haemoderivate GmbH, License No. 258; Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; and Pertussis Vaccine, Typhoid Vaccine, Texas Department of Health Resources, License No. 121.

A list of all voluntarily revoked products reviewed by the Panel, with the date of license revocation, is on file with FDA's Dockets Management Branch (address above). No further regulatory or administrative action is necessary for these products.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsobted, and Diphtheria Antitoxin to Connaught Laboratories, Inc. Connaught Laboratories was issued License No. 711 on January 3, 1978, FDA advises that all comments and recommendations directed to the Merrell-National products apply equally to the products as now manufactured by Connaught Laboratories, Inc.

FDA agrees with the Panel's findings and recommendations for these products, and hereby proposes to adopt its conclusions, including proposed labeling revisions concerning the intended use of the products. Comments or additional data on this classification are invited.

b. *Category II. Biological products determined to be unsafe or ineffective or to be misbranded and which should not continue in interstate commerce:* Streptokinase-Streptodornase (Varidase-buccal tablet, intramuscular, and oral tablet dosage forms), Lederle Laboratories, Division American Cyanamid Co., License No. 17.

Lederle Laboratories was licensed for the manfacture and sale of five forms of Streptokinase-Streptodornase: topical, topical jelly, buccal tablet, intramuscular, and oral tablet. The topical form was recommended for Category I, the topical jelly for Category IIIA, and the buccal tablet, intramuscular, and oral tablet for Category IIIB. At the request of the manufacturer, the product license for the

manufacture and sale of all forms of Streptokinase-Streptodornase has been revoked. Accordingly, no further FDA action is necessary.

c. *Category IIIA.* The Category IIIA classification is a determination that there are concerns about whether the data are sufficient to support an action by the agency to reaffirm or revoke a product license and that, based on an assessment of the present evidence of safety and effectiveness of a product, the potential benefits outweigh the potential risks likely to result from the continued use of a product for a limited period of time. See § 601.25(f)(3).

Under the original procedures for the review of biological products FDA could permit the continued interim marketing of products classified in Category IIIA, provided the manufacturer undertook the necessary additional studies to determine fully the safety and effectiveness of the product. FDA has, however, revised these procedures. The agency decided that it is in the best interest of the public health to reclassify those biologics previously classified in Category IIIA and to proceed either to reaffirm, or to initiate proceedings to revoke, the license for each product. The procedures for implementing this policy were codified under § 601.26 (21 CFR 601.26) by final rulemaking of October 5, 1982 (47 FR 44062).

Under the new procedures, the data for each product classified in Category IIIA will be reviewed by an expert panel to recommend whether:

(i) The product is safe, effective, and not misbranded (Category I) and may remain licensed;

(ii) The product is unsafe, ineffective, or misbranded (Category II) due to the lack of sufficient supportive evidence and for which the product license shall be revoked; or

(iii) The product lacks sufficient supportive evidence of effectiveness (also administratively identified as Category II) but should remain on the market pending the completion of further testing. Such a recommendation may be made only when there is a compelling medical need and no suitable alternative therapeutic, prophylactic, or diagnostic agent is available in sufficient quantity to meet current needs.

Accordingly, FDA has submitted for review by the Vaccines and Related Biological Products Advisory Committee the available data for those licensed products recommended for Category IIIA by the Panel, including those recommended for Category I for booster immunization and Category IIIA for primary immunization. Upon completion of its review, the Advisory Committee will submit a report to FDA containing its conclusions and recommendations for reclassification of the affected products. FDA will respond with a proposal to implement the Advisory Committee's recommendations and will provide an opportunity for public comment at that time. The products classified in Category IIIA are listed below.

(1) *Licensed biological products for which available data are insufficient to classify their safety and effectiveness but which may remain in interstate commerce pending completion of testing:* Pertussis Immune Globulin (Human), Cutter Laboratories, Inc., License No. 8; Pertussis Immune Globulin (Human), Travenol Laboratories, Inc., Hyland Therapeutics Division, License No. 140.

FDA will submit data and information on the two currently licensed Pertussis Immune Globulin (Human) products recommended for Category IIIA to the Vaccines and Related Biological Products Advisory Committee for review and reclassification in accordance with procedures under § 601.26 (21 CFR 601.26).

(2) *Biological product also recommended for Category IIIA but for which the product license has been revoked at the manufacturer's request subsequent to the Panel's review:* Streptokinase-Streptodornase (Varidase, Jelly), Lederle Laboratories, Division of American Cyanamid Co., License No. 17.

d. *Category I and Category IIIA.*

(1) *Licensed biological products recommended by the Panel for Category I when used for booster immunization and for Category IIIA when used for primary immunization:* Tetanus Toxiod, Istituto Sieroterapico Vaccinogeno Toscano Sclavo, License No. 238; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxiods and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use); Tetanus Toxoid, Tetanus Toxoid Adsorbed, Lederle Laboratories, Division American Cyanamid Co., License No. 17; Tetanus Toxoid Adsorbed, Merck Sharp & Dohme, Division of Merck & Co., Inc., License No. 2; Diphtheria and Tetanus Toxoids Adsorbed, Tetanus Toxoid Adsorbed, Michigan Department of Public Health, License No. 99; Tetanus Toxoid Adsorbed, Swiss Serum and Vaccine Institute Berne, License No. 21; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Wyeth Laboratories, Inc., License No. 3.

(2) *Biological products also recommended for Category I when used for booster immunization and for Category IIIA when used for primary immunization but for which the product licenses have been revoked at the manufacturer's request subsequent to the Panel's Review.* Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed (with potassium alum), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Dow Chemical Co., License No. 110; Diphtheria and Tetanus Toxoids, Diphtheria and Tetanus Toxoids Adsorbed, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Eli Lilly and Co., License No. 56; Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Tetanus Toxoid Adsorbed, Merrell-National Laboratories, Division of Richardson-Merrell, Inc., License No. 101; Diphtheria and Tetanus Toxoids, Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine, Tetanus Toxoid, Tetanus Toxoid Adsorbed, Parke-Davis, Division of Warner-Lambert Co., License No. 1; Diphtheria and Tetanus Toxoids Adsorbed, Diphtheria and Tetanus Toxoids and Pertussis Vaccine Adsorbed, Diphtheria Toxoid, Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, Texas Department of Health Resources, License No. 121.

Merrell-National Laboratories, Division of Richardson-Merrell, Inc., transferred its manufacturing processes and facilities for manufacturing Tetanus and Diphtheria Toxoids Adsorbed (For Adult Use), Tetanus Toxoid, and Tetanus Toxoid Adsorbed to Connaught Laboratories, Inc. (The facilities and processes for manufacturing Diphtheria and Tetanus Toxoids and Pertussis Vaccine also were transferred but the license for this product subsequently was revoked voluntarily at the request of Connaught Laboratories, Inc.) FDA issued Connaught Laboratories, Inc., License No. 711 on January 3, 1978. All comments and recommendations concerning these products remain applicable.

The Panel found that until laboratory potency tests for Diphtheria Toxoid and Tetanus Toxoid could be adequately correlated with effectiveness for primary immunization, clincial testing of the toxoid was necessary to demonstrate effectiveness for primary